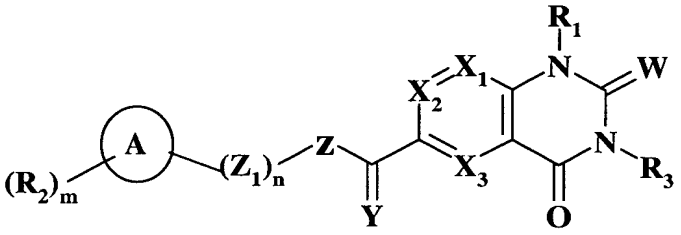
CLAIMS

What is claimed is:

1. A combination, comprising valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric carboxylic inhibitor of MMP-13 of Formula IC



IC

or a pharmaceutically acceptable salt thereof, or an N-oxide thereof,
in which:

$\mathbf{R_1}$ represents a group selected from :

- hydrogen, amino,
- $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$alkenyl, $(C_3\text{-}C_6)$alkynyl, mono$(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, di$(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, heterocycle, and 3- to 6-membered cycloalkyl$(C_1\text{-}C_6)$alkyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, $(C_1\text{-}C_6)$alkyl, cyano, halo$(C_1\text{-}C_6)$alkyl, $C(=O)OR_4$, OR_4 and SR_4, in which R_4 represents hydrogen or $(C_1\text{-}C_6)$alkyl,

W represents an oxygen atom, a sulphur atom, or a group =N-R', in which R' represents $(C_1\text{-}C_6)$alkyl, hydroxyl, or cyano,

$\mathbf{X_1}$, $\mathbf{X_2}$ and $\mathbf{X_3}$ represent, independently of each other, a nitrogen atom or a group -C-R_6 in which R_6 represents a group selected from hydrogen, $(C_1\text{-}C_6)$alkyl, amino, mono$(C_1\text{-}C_6)$alkylamino, di$(C_1\text{-}C_6)$alkylamino, hydroxyl, $(C_1\text{-}C_6)$alkoxy, and halogen,
with the proviso that not more than two of the groups X_1, X_2 and X_3 simultaneously represent a nitrogen atom,

Y represents a group selected from oxygen atom, sulphur atom, -NH, and -N(C_1-C_6)alkyl,

Z represents:

- an oxygen atom, a sulphur atom,
- or a group –NR_7 in which R_7 represents a group selected from hydrogen, (C_1-C_6)alkyl, aryl(C_1-C_6)alkyl, cycloalkyl, aryl, and heteroaryl, and
- when Y is an oxygen atom, a sulphur atom, or a group -N(C_1-C_6)alkyl, Z optionally represents a carbon atom which is unsubstituted or substituted with a (C_1-C_6)alkyl, an aryl, an aryl(C_1-C_6)alkyl, an aromatic or non-aromatic heterocycle or a cycloalkyl,

n is an integer from 1 to 8 inclusive,

Z_1 represents –CR_8R_9 wherein R_8 and R_9, independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, halogen, amino, OR_4, SR_4 or C(=O)OR_4 in which R_4 represents a hydrogen or (C_1-C_6)alkyl, and

- when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one or more multiple bonds,
- and/or one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6)alkyl,
- and when one of the carbon atoms in the hydrocarbon chain Z_1 is replaced with a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, then the group –C(=Y)-Z- optionally may be absent in the general formula (I),

A represents a group selected from :

- aromatic or non-aromatic, 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and

- bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

m is an integer from 0 to 7 inclusive,

the group(s) R_2, which may be identical or different, is (are) selected from (C_1-C_6)alkyl, halogen, -CN, NO_2, SCF_3, $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, $-(CH_2)_kSO_2NR_{10}R_{11}$, $-X_5(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$, $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$, $-(CH_2)_kC(=O)NR_{10}R_{11}$, and $-X_4-R_{12}$ in which:

- X_5 represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen atoms, and nitrogen substituted by hydrogen or (C_1-C_6)alkyl,

- k is an integer from 0 to 3 inclusive,

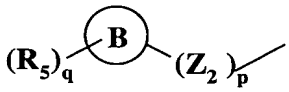
- R_{10} and R_{11}, which may be identical or different, are selected from hydrogen and (C_1-C_6)alkyl,

- X_4 represents a group selected from single bond, $-CH_2-$, oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or (C_1-C_6)alkyl group,

- R_{12} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6)alkyl, halogen, hydroxyl and amino, and when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur;

R_3 represents a group selected from:

- hydrogen,
- (C_1-C_6)alkyl, (C_3-C_6)alkenyl, (C_3-C_6)alkynyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, cyano, halo(C_1-C_6)alkyl, cycloalkyl, -$C(=O)NR_{10}R_{11}$, -$C(=O)OR_{10}$, OR_{10}, and SR_{10}, in which R_{10} and R_{11}, which may be identical or different, represent hydrogen or (C_1-C_6)alkyl,
- and the group of formula :



✓ in which p is an integer from 0 to 8 inclusive,

✓ Z_2 represents -$CR_{13}R_{14}$ wherein R_{13} and R_{14}, independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl, phenyl, halo(C_1-C_6)alkyl, halogen, amino, OR_4, SR_4 and -$C(=O)OR_4$ in which R_4 represents hydrogen or (C_1-C_6)alkyl, and

- when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one or more multiple bonds,
- and/or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6)alkyl, or a carbonyl group,

✓ B represents a group selected from:

- an aromatic or non-aromatic 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and
- a bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

✓ q is an integer from 0 to 7 inclusive,

✓ the group(s) R_5, which may be identical or different, is (are) selected from $(C_1\text{-}C_6)$alkyl, halogen, CN, NO_2, CF_3, OCF_3, $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$, $-C(=O)O-(CH_2)_{k2}-C(=O)OR_{18}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, $-(CH_2)_kC(=O)NR_{15}R_{16}$, $-R_{19}-C(=O)OR_{15}$, $-X_6-R_{20}$, and $-C(=O)-R_{21}-NR_{15}R_{16}$ in which :

- X_7 represents a group selected from oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by a hydrogen atom or a $(C_1\text{-}C_6)$alkyl group,

- k is an integer from 0 to 3 inclusive,

- k1 is an integer from 0 to 2 inclusive,

- k2 is an integer from 1 to 4 inclusive,

- R_{15}, R_{16} and R_{17}, which may be identical or different, are selected from hydrogen and $(C_1\text{-}C_6)$alkyl,

- R_{18} represents a group selected from $(C_1\text{-}C_6)$alkyl, $-R_{21}-NR_{15}R_{16}$, $-R_{21}-NR_{15}-C(=O)-R_{21}-NR_{16}R_{17}$, and $-C(=O)O-R_{21}-NR_{15}R_{16}$ in which R_{21} represents a linear or branched $(C_1\text{-}C_6)$alkylene group, and R_{15}, R_{16} and R_{17} are as defined hereinbefore,

- R_{19} represents a $(C_3\text{-}C_6)$cycloalkyl group,

- X_6 represents a group selected from single bond, $-CH_2-$, oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or $(C_1\text{-}C_6)$alkyl group,

- R_{20} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from $(C_1\text{-}C_6)$alkyl, halogen, hydroxyl, oxo, cyano, tetrazole, amino, and -$C(=O)OR_4$ wherein R_4 represents hydrogen or $(C_1\text{-}C_6)$alkyl, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

with the proviso that when X_1 represents a nitrogen atom, X_2 cannot represent a carbon atom substituted with a methyl group or with $NH\text{-}CH_3$.

2. The combination according to Claim 1, wherein the compound of Formula IC is selected from:

4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;

3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide;

Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoate;

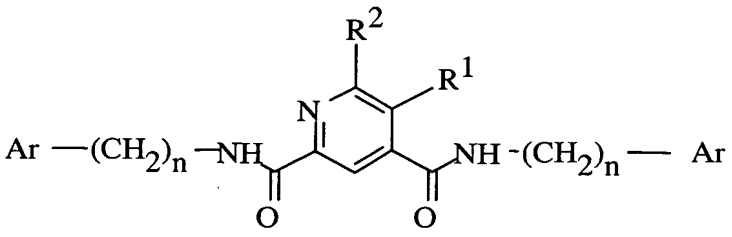
3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide;

4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;

4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid;

or a pharmaceutically acceptable salt thereof.

3. A combination, comprising valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric carboxylic inhibitor of MMP-13 of Formula VG



VG

or a pharmaceutically acceptable salt thereof, wherein

R^1 and R^2 independently are hydrogen, halo, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, NO_2, NR^4R^5, CN, or CF_3;

n is 1, and

Each Ar independently is aryl or Het, wherein aryl is phenyl or substituted phenyl, and Het is an unsubstituted or substituted heteroaryl group.

4. A pharmaceutical composition, comprising a combination of valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric carboxylic inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

5. A method of treating a disease or disorder selected from cartilage damage, inflammation, arthritis, and pain in a mammal, comprising administering to the mammal a therapeutically effective amount of a combination of valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric carboxylic inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.

6. The method according to Claim 5, wherein the disease or disorder is rheumatoid arthritis.

7. The method according to Claim 5, wherein the disease or disorder is osteoarthritis.

8. The method according to Claim 5, wherein the disease or disorder is joint inflammation.

9. The method according to Claim 5, wherein the pain is joint pain.